

Background

- Brain connectivity research has traditionally focused on diffusion MRI, resting-state fMRI, EEG, and MEG to characterise structural and functional connections
- Positron Emission Tomography provides a complementary molecular perspective enabling the in vivo quantification of regional substrates such as metabolism, neurotransmission, and proteinopathies

Rationale & Research Questions

- In Alzheimer's Disease, Amyloid-Beta (Aβ) PET enables the in vivo quantification of the Aβ plaque formation
- Methodological approaches for constructing single-subject Aβ PET connectomes are limited, yet several analytical decisions may impact the resulting connectomes

How to construct single-subject Aβ connectomes?

Which is the most robust and biologically meaningful connectome configuration?

Connectomes Construction Options

Amyloid Quantification Metric

Standardised Uptake Value Ratio (SUVR)

- cerebellum as reference region
- default normalisation

Voxel-wise z-score (z-low)

- low - Aβ uptake ref subset
- regional healthy load

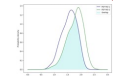
Voxel-wise z-score (z-high)

- high - Aβ uptake ref subset
- regional maximum capacity

Regional signal extraction and inter-regional similarity metric

Kullback-Leibler Divergence Similarity Estimation (KLSE)

- For each region: estimation of the voxel-value distribution using Gaussian-kernel density estimation (KDE)
- For each pair of regions i, j : computation of the symmetrized Kullback-Leibler divergence and derivation of a bounded similarity score between 0 and 1



Effect Size approach (ES)

- For each region: computation of the deviation from the regional mean of the low Aβ uptake ref. subset

$$ES(i, j) = \frac{(x_i - x_{i,low}) - (x_j - x_{j,low})}{\sqrt{\sigma_i^2 + \sigma_j^2}}$$

- For each pair of regions i, j :
Effect-Size calculation
Bounded similarity score between 0 and 1
Modulation of the low-group correlation matrix G

$$w(i, j) = 1 - \tanh(ES(i, j))$$

$$c(i, j) = \sqrt{w(i, j) \cdot G(i, j)}$$

Parcellation Schemes

Anatomically defined Functionally defined

Desikan-Killiany

Schaefer-100



Schaefer-100



Machine Learning Framework

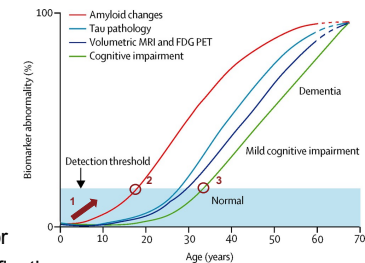
- Ten connectomes were generated for each subject
- Connectome configurations were compared based on their predictive performance on AD-related outcomes

Clinical Outcomes

- Detectable amyloid accumulation (Annualized Rate Of Change > 3 CL)
- Progression in Aβ-status (Baseline to follow-up CL > 24)
- Progression in CDR score (0 to ≥0.5)

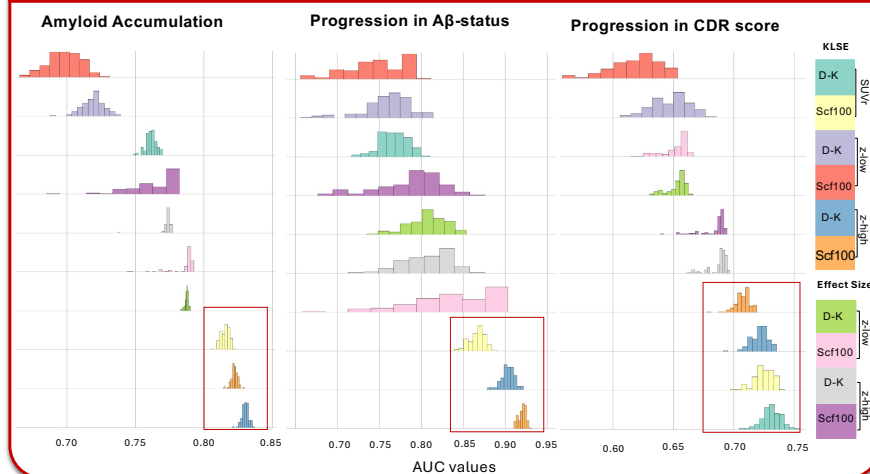
Connectome Predictive Modelling

- Edge-wise correlation with the outcome vector
- Selection of FDR-significant edges and identification of pos and neg edge sets
- Subject-level averaging of pos and neg edge strengths
- Logistic regression using two CPM features

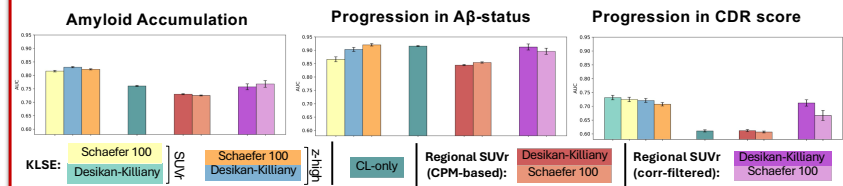


100 repetition of stratified 5-fold cross validation
Performance evaluation using ROC-AUC

Predictive Performances



Comparison with Centiloid and Regional SUVR models



Results & Conclusions

- Optimal connectome configurations depends on the clinical outcome of interest
- KLSE connectomes outperform Effect Size connectomes, while SUVR and z-high maps outperform z-low maps; atlas choice had limited impact on predictive performance
- Connectome-based models improved prediction of amyloid accumulation and progression in CDR score with CL-only and regional SUVR-based models, while performance for Aβ-status conversion remain comparable across approaches
- Single-subject connectomes capture biologically meaningful information beyond global and regional Aβ-burden
- Amyloid-Beta connectomes from static PET imaging may provide complementary biomarkers for tracking early AD-related progression

